

The Use of Intravenous Immunoglobulin in Autoimmune Bullous Diseases

Shien-Ning Chee, MBBS (UNSW)^{a,b},
Dédée F. Murrell, MA, BMBCh, FAAD, MD, FACD^{c,*}

KEYWORDS

- Intravenous immunoglobulin • Pemphigus
- Autoimmune bullous disease • Inflammatory disease

Autoimmune blistering diseases (AIBD) are a rare group of diseases that affects the skin and mucous membranes. They tend to be chronic remitting conditions, which have implications on best treatment and quality of life. AIBD includes pemphigus and its subtypes: bullous pemphigoid (BP), linear IgA bullous dermatosis, mucous membrane pemphigoid (MMP), and epidermolysis bullosa acquisita (EBA). There are two major categories dependent of whether the blistering is intraepidermal (pemphigus) or subepidermal (BP).

The mainstay of treatment of AIBD is corticosteroids, with doses and route of administration dependant on the type of AIBD. With exacerbations and relapses of blistering, the dose of prednisone is increased and, later, slowly tapered according to clinical response. Other immunosuppressive agents are used for a steroid-sparing effect because corticosteroids cause a significant number of side effects, including immune suppression, diabetes mellitus, osteoporosis, myopathy, cataracts, hypertension, mood changes, and peptic ulcer disease, all of which add to disease burden. Immunosuppressive agents often used include azathioprine and mycophenolate. However, these in turn have their own side effects, including bone marrow suppression, which may lead to anemia, leucopenia and thrombocytopenia, and liver

A version of this article was previously published in *Dermatologic Clinics* 29:4.

^a Department of Dermatology, St George Hospital, Gray Street, Kogarah, Sydney, NSW 2217, Australia; ^b Faculty of Medicine, University of New South Wales, High Street, Kensington, Sydney, NSW 2052, Australia; ^c Department of Dermatology, St George Hospital, University of New South Wales, Gray Street, Kogarah, Sydney, NSW 2217, Australia

* Corresponding author.

E-mail address: d.murrell@unsw.edu.au

Immunol Allergy Clin N Am 32 (2012) 323–330

doi:[10.1016/j.iac.2012.04.012](https://doi.org/10.1016/j.iac.2012.04.012)

immunology.theclinics.com

0889-8561/12/\$ – see front matter © 2012 Elsevier Inc. All rights reserved.

function abnormalities. Intravenous immunoglobulin (IVIG) is a third-line adjunctive approach to treat AIBD unresponsive to conventional therapy.¹

INTRODUCTION TO IVIG

IVIG is made of IgG fractionated from pooled plasma, via whole blood donors or by plasmapheresis. Since its introduction in the 1950s in subcutaneous or intramuscular form, and its availability in intravenous (IV) form in the 1980s, administration has increased dramatically for a wide variety of diseases. It is used mainly in two situations. First, as replacement therapy in patients with antibody deficiency diseases—these are usually genetic conditions that have onset in early childhood. The second use is in autoimmune or inflammatory diseases.²

Each plasma pool of IVIG ranges from 4000 to 50,000 L, preferably from more than 1000 donors per lot. IVIG lots are not identical, with each containing varying amounts of IgG subclasses and other proteins and immunoglobulins such as albumin, IgA, IgE, and IgM.³ Each step in production (fractionation, purification, stabilization, viral inactivation, formulation) and the varying plasma sources can exert an influence on the final product, including an effect on the biologic activity of the IgG molecule.³

The majority of side effects, including headache, nausea, fever, and cough, are transient and do not require discontinuation of therapy. Most of these are preventable by the administration of oral antihistamines before the infusion or slowing of the infusion rate. However, rare and potentially fatal adverse events include anaphylactic reactions, aseptic meningitis, acute renal failure, cardiovascular compromise from fluid overload, and thromboembolic events such as cerebral infarction and pulmonary emboli. Adverse effects may be related to factors such as concentration of the IVIG (thus affected volume load) and osmolality (mostly due to sodium and sugar content, possibly affecting thromboembolic events).^{3,4} There are also social problems related to the use of IVIG. It is a very expensive drug, with laboratory tests, infusion equipment, and facility fees adding to the cost. It is also time consuming, with patients having to travel and take time from their normal activities for infusions.⁵ The concentration of IVIG is usually 5% to 6%.⁶ A higher concentration allows for smaller volumes, which is useful in patients who have conditions such as heart failure where fluid balance is a concern. Most are delivered by IV infusions, but it may also be given subcutaneously. Subcutaneous administration is helpful in patients who experience severe rate-related adverse reactions, have poor venous access, or want the convenience of self-administration. The monthly IV dose is converted into grams, then milliliters, for weekly subcutaneous administration. A subcutaneous dose of 137% of the IV dose may be needed to achieve a comparable metabolic rate. Adults usually tolerate 15 to 20 mL per infusion site.⁷

Pemphigus

Pemphigus is characterized by loss of adhesion between keratinocytes, giving rise to blister formation. This loss of adhesion is due to auto-antibodies directed against intercellular adhesion structures (acantholysis). The subtypes of pemphigus may be distinguished by the specificity of the auto-antibodies for different targets or by the location of blister formation. In the most common form, pemphigus vulgaris (PV), blisters are located just above the basal skin layer. The hallmark is flaccid blisters that easily rupture to leave denuded painful erosions, often with oral involvement. With pemphigus foliaceus (PF), blisters occur within the granular layer of the epidermis. There are superficial blisters that easily rupture to leave superficial erosions. Cutaneous involvement is often more extensive than in PV, but mucous membrane

involvement is uncommon. Other pemphigus variants include paraneoplastic and drug-induced pemphigus. The titer of autoantibodies detected by indirect immunofluorescence microscopy and ELISA against desmogleins 1 and 3 in pemphigus is related to disease activity.^{1,8}

IVIg is believed to work by rapidly and selectively lowering serum levels of these pathogenic antibodies that mediate pemphigus. This may be achieved by increasing catabolism of the immunoglobulin molecules. Cytotoxic agents given in conjunction with IVIg may reduce the rebound increase in levels of the depleted antibody after administration of IVIg.⁹ Typically, pemphigus patients commenced on IVIg as a third-line treatment are given IVIg in addition to their oral corticosteroid and oral adjunctive agent, to which they were not responding adequately.

There have been numerous small studies, investigating the use of IVIg in PV and PF. In general, these studies show that IVIg is effective, even more so when administered concurrently with a cytotoxic drug such as cyclophosphamide or azathioprine. The addition of a cytotoxic drug is thought to offset the rebound in the level of antibodies that occurs after IVIg treatment.⁹⁻¹¹ However, these studies were not all placebo-controlled, randomized, or double-blinded.

The first placebo-controlled study investigating the use of IVIg in PV involved a single patient who had multiple relapses of PV despite treatment with steroids and adjunctive immunosuppressants. The patient was never disease-free and had many complications related to steroid use, including diabetes, osteopenia, ruptured tendons, and cutaneous infections secondary to immunosuppression. In 2004, all adjuvant therapies except azathioprine were discontinued, and he was placed on 140 g (2 g/kg) IVIg fortnightly for eight infusions, which led to dramatic improvement and allowed for a reduction in prednisolone from 45 to 30 mg daily. He was maintained on 80 g (1 g/kg) of IVIg monthly for 16 months. Thereafter, a formal randomized, double-blind, placebo-controlled, crossover trial was commenced. There were two phases of the trial, each consisting of 6 consecutive months of either IVIg 1 g/kg or placebo infusion. Prednisolone was continued during the trial with instructions given to the patient to taper the dose by 5 mg decrements at fortnightly intervals when lesions became quiescent and azathioprine was continued throughout at an unchanged dose. The mean subjective patient disease scores were much improved with IVIg compared with placebo (mean overall score of 11.6 vs 20.6). Also improved were pemphigus autoantibody titers (1:20 on placebo vs 1:80 with IVIg), desmoglein 3 antibody levels (79 vs 126), and desmoglein 1 antibody levels (94 vs 126). On placebo, the mean dose of prednisolone was 33.7 compared with 35.8 mg on IVIg, which is of questionable significance because there was no attempt in the protocol to taper the steroid using a standard method during the 6-month periods.¹⁰

There has been only one multicenter, randomized, placebo-controlled, double-blinded trial conducted in pemphigus vulgaris that were unresponsive to standard treatments or relapsing. This study was based in Japan, using patients who were unresponsive to prednisone doses over 20 mg/day. It investigated the effect of a single 5-day cycle of IVIg. Twenty-one patients were given 400 mg IVIg daily (2 g over 5 days; for a 70 kg patient equivalent to 2.5 mg/kg), 20 were given 200 mg IVIg daily, and 20 were given a placebo identical solution. There was a significant difference between the 400 mg and placebo groups in terms of therapeutic endpoint, defined as time to escape from the protocol (a novel efficacy indicator). There was also improvement with 200 mg versus placebo, but this did not reach statistical significance. Clinical severity improved significantly with both 400 mg and 200 mg compared with placebo, though the 200 mg group needed an additional 42 days to reach the same level of improvement as the 400 mg group. Antidesmoglein 3 IgG autoantibodies decreased

significantly with 400 mg, decreased slightly with 200 mg, and not at all with placebo. Unlike most previous studies that suggest efficacy of IVIG for treatment of pemphigus with multiple treatment cycles, Amagai and colleagues¹² (2009) show that a single 5-day cycle has therapeutic benefits.

BP

IVIG has been reported only in uncontrolled studies of BP and found to be somewhat effective. One study investigated 15 patients who had with relapsing BP despite treatment with prednisone or systemic therapies. Data was collated regarding prednisone regimes, side effects from treatment, hospital admissions, disease activity, and quality of life as measured on a five-point Likert scale. IVIG was then initiated at 2 g/kg over 3 days every 4 weeks and prednisone and adjuvant treatments were tapered. However, patients had twice daily baths or normal saline compresses to remove skin debris followed by medium-strength topical corticosteroid cream applied to improve healing and any lesions unresponsive to topical therapy were treated with sublesional injections of 15 to 20 mg/ml of triamcinolone acetonide. This practice could have compounded the assessment of the IVIG, because topical steroids have since been shown to be effective for BP. Hence, the conclusions on demonstration of efficacy are limited from this study.¹³

Another study, coordinated by Ahmed and colleagues (2003),¹⁴ involved 10 patients with severe BP. Serum samples were collected monthly over the study duration of 18 months to measure autoantibody titers. IVIG was administered at 4-week intervals at 2 g/kg per cycle until all lesions had healed. Thereafter the intervals between cycles were gradually increased to 6, 8, 10, 12, and 16 weeks. The mean autoantibody titers before IVIG were 2600 for BP Ag1 and 2380 for BP Ag2. After 3 months of treatment, there was clinical improvement with a statistically significant decrease in mean autoantibody titers. After 11 months, autoantibody tires became nondetectable and lesions had completely healed with no new lesions. Serologic remission was sustained for an average of 7 months with no new blister formation seen for the remainder of the study. Antibody titers to tetanus toxoid were used as controls and no change in tetanus toxoid levels was observed during the study. There was also a control group consisting of seven patients with BP in remission, seven patients with PV, and 15 healthy individuals. Antibody titers to BP Ag1 and Ag2 were nondetectable in the control group. This was the first study demonstrating the serologic response of two autoantibodies to BP when IVIG is administered. It is unknown if the patients were taking steroids or immunosuppressants before or during the study, or if their disease had been refractory to other treatments.¹⁴ The two above studies also originate from the same study center and patient registry numbers are unavailable for tracking.

Bystryn and colleagues (2008)¹⁵ suggest IVIG to be effective only when administered with an immunosuppressive agent. One patient with BP refractory to prednisone and mycophenolate mofetil was commenced on three cycles of IVIG given 3 weeks apart. Serum IgG decreased from 320 to 20, serum IgG4 decreased from 640 to 80 existing lesions completely cleared, and no new lesions developed. Several months later mycophenolate mofetil had been ceased and prednisone tapered to 5 mg/daily. Three cycles of IVIG every 2 weeks was administered with prednisone alone, with no improvement. In fact, serum titers of pemphigoid IgG remained unchanged, levels of IgG4 doubled, and the patient experienced one flare of disease with several new bullae. Azathioprine 150 to 200 mg/day was then added and, after four cycles of IVIG every 2 weeks, serum IgG and IgG4 halved. With another 6 cycles of IVIG, autoantibody levels decreased fourfold. However, disease activity did not correlate because there were several new bullae. Azathioprine was then ceased and IVIG

was given with prednisone alone. IgG and IgG4 titers quadrupled over 3 months with an average of one new blister per week. Administration of an immunosuppressive agent with IVIG and prednisone appears to be more effective than IVIG and prednisone alone.¹⁵

IVIG may also be useful as monotherapy in childhood BP. A 3-month-old boy with BP was unresponsive to prednisone (2.8 mg/kg/day), dexamethasone, erythromycin, and dapsone, with new blisters and erythema over the whole body. After 2 months in hospital trialing the above treatments, a 5-day course of IVIG (300 mg/kg/day) was commenced in addition to dexamethasone 0/75 mg/day, erythromycin, and dapsone. After 4 days, no new skin lesions developed. One week later, skin lesions were much improved allowing for tapering of dexamethasone and discontinuation of erythromycin. A month later there was recurrence of blistering and a second course of IVIG was given, resulting in improvement, which allowed for discontinuation of dapsone and complete tapering of dexamethasone 7 months later. At follow-up 16 months later, there had been no relapse.¹⁶ Another case involved a Chinese, 3-month-old boy with BP and eczema, whose parents refused systemic steroid therapy. IVIG 400 mg/kg/day was given for 4 days with cefaclor. Erythema and most bullae over the body resolved within 1 week. Within the next year, there were several mild relapses of blisters that were controlled with oral antihistamines and topical corticosteroids. In the following 2 years, there were no relapses of bullae.¹⁷

MMP

MMP affects the mucous membranes of the body, including the oral cavity, ocular membranes, nose, pharynx, larynx, trachea, and genitalia. Ocular involvement can ultimately lead to blindness.¹⁸

There has been one comparison study involving 18 patients with ocular MMP. Eight patients were treated with IVIG, and then compared with eight other patients on conventional immunosuppressive therapy who had identical disease (duration and severity) and were matched for age and sex. The IVIG group was given 2 g/kg per cycle of 2 to 4 week intervals. Once clinical improvement was observed and disease had stabilized, the previous systemic conventional therapy was discontinued, but the method for tapering was not specified. IVIG continued for 16 weeks. Conventional therapy differed between patients, including agents such as prednisone, diaminodiphenylsulfone (dapsone), methotrexate, azathioprine, or mycophenolate mofetil. All patients in the IVIG group had total control of disease at 24 months with no progression of disease, while the other group had disease progression despite using conventional therapy at adequate doses for recommended periods of time. IVIG users also had faster control of ocular inflammation and no relapses, unlike patients on conventional therapy. Letko and colleagues¹⁹ (2004) suggest that ocular MMP should be an indication for IVIG treatment.

Another pilot study of six patients with severe ocular involvement unresponsive to conventional therapy also demonstrated the efficacy of IVIG (cycles of 2 g/kg over 3 days), with rapid improvement in symptoms and signs such as conjunctival erythema, photophobia, and discomfort. No patients had a decrease in their disease staging and two patients had an improvement. This study is continuing, investigating the durability of long-term remission.²⁰

Three other case studies have found IVIG to be effective in recalcitrant MMP. In these studies, IVIG was given in addition to steroids with or without immunosuppressants. Two studies used IVIG 1 g/kg/daily for 2 to 3 days. One study did not quantify the amount of IVIG given.²¹⁻²³

EBA

EBA is characterized by inflammatory or noninflammatory blisters at sites of trauma that affect the collagen VII under the lamina densa, thus leading to milia and scar formation. There are various types of EBA, some of which resemble BP or MMP.¹ There have been few case studies on the use of IVIG in EBA.

One study involving a 16-year-old boy showed that high-dose IVIG (400 mg/kg/day for 4 days repeated every 2 weeks) led to good clinical improvement when administered with cyclosporin and prednisone. However, there was no decrease in circulating autoantibodies.²⁴ There have been two studies investigating high-dose IVIG without concomitant use of steroids or immunosuppressants. One of these studies showed improvement after two cycles of IVIG (400 mg/kg/day for 5 days) with healing of most erosions and few new blisters. Six months after the sixth and final cycle, the condition was still in remission.²⁵ However, the other study showed no improvement in disease either clinically or by measurement of autoantibodies.²⁶

Low-dose IVIG is an alternative that allows for reduced costs and side effects. One patient with EBA refractory to steroids, immunosuppressants, colchicine, and plasmapheresis was commenced on IVIG at 40 mg/daily in 3-day cycles repeated every 3 to 4 weeks, coadministered with prednisone. After four cycles, no new blisters appeared and lesions started healing. One year later, prednisone was discontinued and the interval between IVIG infusions was extended to 6 weeks. To the time of publication of the case-study, the patient remained disease-free and continued to receive low-dose IVIG every 6 weeks.²⁷

IVIG has also successfully been administered subcutaneously. One patient with EBA resistant to corticosteroids, azathioprine, mycophenolate mofetil, mercaptopurine, minocycline, and plasmapheresis was given two boluses of 1.7 g/kg IVIG at 8 weekly intervals, followed by divided doses every 3 weeks. Treatment was changed to subcutaneous immunoglobulin (SCIG) due to poor venous access and convenience of self-treatment at home. Throughout treatment with both IVIG and SCIG, there was reduction of symptoms and gradual withdrawal of all immunosuppressive therapy. Maintenance was achieved with SCIG at 0.9 g/kg/month given in divided doses on 5 days per week. Circulating autoantibodies reduced from 1:16 to zero on intact skin, and 1:32 to 1:10 on salt split skin testing. Subcutaneous administration may be a good alternative in patients with poor venous access, or those who wish to be able to administer their medication at home.²⁸

SUMMARY

IVIG has been shown to be effective in the treatment of AIBD and may be an option if disease is refractory to conventional treatment. Effectiveness of IVIG appears to increase when administered concurrently with a cytotoxic drug. Most reports use multiple treatment cycles, though single cycles may give benefit. Tapering IVIG administration may improve the duration of remission and subcutaneous injections may be an option if IVIG is inconvenient or inappropriate.

There is a need for well-conducted, randomized, placebo-controlled double-blinded trials investigating the use of IVIG in AIBD, particularly in BP, MMP, and EBA, so that patients can receive good, evidence-based care. Issues requiring more investigation include

- Optimal IVIG doses and regimens (eg, number of cycles, intervals between cycles, use of tapering of IVIG, when IVIG should be first commenced)
- Benefits of adjuvant immunosuppressive agents
- Relative benefits of agents

Cost-effectiveness

Effectiveness of IVIG in modification or suppression of the course of disease.

REFERENCES

1. Ahmed A. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006;6:557–78.
2. Gelfand E. Differences between IGIV products: impact on clinical outcome. *Int Immunopharmacol* 2006;6:592–9.
3. Martin T. IGIV: contents, properties, and methods of industrial production—evolving closer to a more physiologic product. *Int Immunopharmacol* 2006;6: 517–22.
4. Feldmeyer L, Benden C, Haile S, et al. Not all intravenous immunoglobulin preparations are equally well tolerated. *Acta Derm Venereol* 2010;90(5):494–7.
5. Dahl M, Bridges A. Intravenous immune globulin: fighting antibodies with antibodies. *J Am Acad Dermatol* 2001;45(5):775–84.
6. Red Cross Australia. Appendix 1 - Comparison of INTRAGAM P, Flebogamma 5% DIF and Octagam. 2011. Available at: <http://www.transfusion.com.au/sites/default/files/Comparison%20between%20IVIG%20products%20-%20Final.pdf>. Accessed June 24, 2011.
7. Ballow M. Immunoglobulin therapy: methods of delivery. *J Allergy Clin Immunol* 2008;122(5):1038–9.
8. Noursari H, Anhalt G. Pemphigus and bullous pemphigoid. *Lancet* 1999;354: 667–72.
9. Lolis M, Toosi S, Czernick A, et al. Effect of intravenous immunoglobulin with or without cytotoxic drugs on pemphigus intercellular antibodies. *J Am Acad Dermatol* 2011;64(3):484–9.
10. Arnold D, Burton J, Shine B, et al. An 'n-of-1' placebo-controlled crossover trial of intravenous immunoglobulin as adjuvant therapy in refractory pemphigus vulgaris. *Br J Dermatol* 2009;160(5):1098–102.
11. Bystryń J, Jiao D, Natow S. Treatment of pemphigus with intravenous immunoglobulin. *J Am Acad Dermatol* 2002;47(3):358–63.
12. Amagai M, Ikeda S, Shimizu H, et al. A randomised double-blind trial of intravenous immunoglobulin for pemphigus. *J Am Acad Dermatol* 2009;60(4):595–603.
13. Ahmed A. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001;45(6):825–35.
14. Sami N, Ali S, Bhol K, et al. Influence of intravenous immunoglobulin therapy on autoantibody titres to BP Ag1 and BP Ag2 in patients with bullous pemphigoid. *J Eur Acad Dermatol Venereol* 2003;17:641–5.
15. Czernik A, Bystryń J. Improvement of intravenous immunoglobulin therapy for bullous pemphigoid by adding immunosuppressive agents. *Arch Dermatol* 2008;144(5):658–61.
16. Sugawara N, Nagai Y, Matsushima Y, et al. Infantile bullous pemphigoid treated with intravenous immunoglobulin therapy. *J Am Acad Dermatol* 2007;57(6): 1084–9.
17. Xiao T, Li B, Wang Y, et al. Childhood bullous pemphigoid treated by i.v. immunoglobulin. *J Dermatol* 2007;34:650–3.
18. Chan L, Ahmed A, Anhalt G. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment and prognostic indicators. *Arch Dermatol* 2002;138:370–9.

19. Letko E, Miserocchi E, Daoud Y, et al. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. *Clin Immunol* 2004;111:303–10.
20. Mignogna M, Leuci S, Piscopo R, et al. Intravenous immunoglobulins and mucous membrane pemphigoid [letter]. *Ophthalmology* 2008;115(4):752, e751.
21. Galdos M, Etxebarria J. Intravenous immunoglobulin therapy for refractory ocular cicatricial pemphigoid: case report. *Cornea* 2008;27(8):967–9.
22. Leverkus M, Georgi M, Nie Z, et al. Cicatricial pemphigoid with circulating IgA and IgG autoantibodies to the central portion of the BP180 ectodomain: beneficial effect of adjuvant therapy with high-dose intravenous immunoglobulin. *J Am Acad Dermatol* 2002;46:116–22.
23. Iaccheri B, Roque M, Fiore T, et al. Ocular cicatricial pemphigoid, keratomycosis, and intravenous immunoglobulin therapy. *Cornea* 2004;23:819–22.
24. Meier F, Soninichsen K, Schaumburg-Lever G, et al. Epidermolysis bullosa acquisita: efficacy of high-dose intravenous immunoglobulins. *J Am Acad Dermatol* 1993;29(2):334–7.
25. Gourgiotou K, Exadaktylou D, Aroni K, et al. Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol* 2002;16:77–80.
26. Caldwell M, Yancey K, Engler R, et al. Epidermolysis bullosa acquisita: Efficacy of high-dose intravenous immunoglobulins [letter to the editor]. *J Am Acad Dermatol* 1994;31(5):827–8.
27. Kofler H, Wambacher-Gasser B, Topar G, et al. Intravenous immunoglobulin treatment in therapy-resistant epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1996;36(2):331–5.
28. Tayal U, Burton J, Chapel H. Subcutaneous immunoglobulin therapy for immunomodulation in a patient with severe epidermolysis bullosa acquisita [letter to the editor]. *Clin Immunol* 2008;129:518–9.